

PRESS RELEASE

EACS 2019: ViiV Healthcare to present 17 abstracts from its portfolio addressing the diverse needs of people living with HIV

Data presentations expand understanding of ViiV Healthcare's pipeline for heavily treatment-experienced populations, and look deeper into its 2-drug regimen studies

London, 6 November 2019 – [ViiV Healthcare](#), the global specialist HIV company majority-owned by GSK, with Pfizer Inc. and Shionogi Limited as shareholders, announced today that 17 abstracts from its portfolio of late-stage pipeline and approved HIV treatments will be presented at the [17th European AIDS Conference \(EACS 2019\)](#) in Basel, Switzerland, 6-9 November.

Advances in research and development combined with the availability of effective medicines are changing the HIV landscape beyond 3-drug regimens which have been the mainstay of HIV treatment. ViiV Healthcare has been an integral part of this shift with the development of the 2-drug regimens (2DR) Dovato* (dolutegravir/lamivudine) and in partnership with Janssen, Juluca (dolutegravir/rilpivirine). Together with Janssen, ViiV healthcare is also working on cabotegravir and rilpivirine long-acting, an investigational long-acting injectable regimen. We are continuing to expand our innovative treatment portfolio by developing fostemsavir, a first-in-class treatment for people living with HIV (PLHIV) who have very few or no treatment options left available to them.

Kimberly Smith, MD, Head of Research & Development at ViiV Healthcare, said: "Since ViiV Healthcare's inception 10 years ago, we have used our experience in drug development and the time we have spent getting to know people living with HIV to create research into innovative treatments that meet their diverse and changing needs. At EACS 2019, we are presenting data that take a deeper look at how different populations, including women and those who are heavily treatment-experienced, can benefit from our treatment innovations, to give us a fuller understanding of outcomes in these populations."

* Dovato (dolutegravir/lamivudine) is not approved in Switzerland

Key ViiV Healthcare abstracts to be presented at EACS 2019

Presenting data for ViiV Healthcare's long-acting cabotegravir and Janssen's rilpivirine in women

- Efficacy rates of long-acting cabotegravir and rilpivirine in women at Week 48, from the pooled ATLAS and FLAIR studies¹

Expanding our understanding of fostemsavir in heavily treatment-experienced (HTE) PLHIV

- Genotypic and phenotypic results for fostemsavir in HTE participants with HIV-1 at 96 weeks, from the phase 3 BRIGHT study²
- Impact of susceptibility scoring on virologic response in HTE participants with HIV-1 on a fostemsavir-based regimen: week 96 results from the phase 3 BRIGHT study³

Further data for Dovato[†] 2DR from the landmark GEMINI and TANGO studies

GEMINI 1 & 2 studies

- Assessments of very low-level HIV replication for dolutegravir and lamivudine vs dolutegravir + tenofovir disoproxil/emtricitabine (TDF/FTC) in the GEMINI 1 & 2 studies through week 96⁴

TANGO study

- Week 48 subgroup analysis assessing efficacy outcomes in participants on dolutegravir/lamivudine versus a tenofovir alafenamide (TAF)-based regimen⁵
- Week 48 data showing that switching to dolutegravir/lamivudine from a 3-drug TAF-based regimen was not associated with a higher frequency of intermittent viremia⁶

Treatment outcomes in real-world populations: continuing to evaluate effectiveness post-approval for Juluca 2DR

Real-world evidence comparing Juluca (dolutegravir/rilpivirine) to standard 3-drug regimens⁷

[†] Dovato (dolutegravir/lamivudine) is not approved in Switzerland

The full list of data that will be presented by ViiV Healthcare at EACS 2019 is listed below:

Cabotegravir and rilpivirine long-acting regimen

Format	Title of abstract	Author/ presenter	Abstract/ poster number	Time (CET)/ location
Oral	Outcomes for women in phase 3 trials of long-acting cabotegravir + rilpivirine: pooled ATLAS & FLAIR week 48 results	Romina Quercia	PS1/1	Event Hall 7 Nov 10:20-10:35

Dovato (dolutegravir/lamivudine)*

Format	Title of abstract	Author/ presenter	Abstract/ poster number	Time (CET)/ location
Oral	Assessments of very low-level HIV replication for dolutegravir + lamivudine (DTG+3TC) vs dolutegravir + tenofovir disoproxil/emtricitabine (DTG+TDF/FTC) in the GEMINI 1 & 2 studies through week 96	Mark Underwood	PS8/2	Event Hall 8 Nov 10:15 – 10:30
Oral	Switching to DTG/3TC fixed dose combination (FDC) is non-inferior to continuing a TAF-based regimen (TBR) through 48 weeks: subgroup analyses from the TANGO study	Jean van Wyk	PS7/2	Boston 1 – 3 7 Nov 14:20 - 14:40
ePoster	Switching from a 3-drug tenofovir alafenamide (TAF)-based regimen (TBR) to a 2-drug dolutegravir/lamivudine (2DR, DTG/3TC FDC) was not associated with a higher frequency of intermittent viremia in suppressed patients in the TANGO study	Ruolan Wang	PE3/15	Exhibition hall 6 Nov 12:45 – 20:00 7 Nov 9:00 – 18:00 8 Nov 9:00 – 18:00

Dolutegravir

Format	Title of abstract	Author/ presenter	Abstract/ poster number	Time (CET)/ location
Oral	Dolutegravir (DTG) use during pregnancy and birth outcomes: data from the antiretroviral pregnancy registry (APR)	Vani Vannappagari	PS1/2	Event Hall 7 Nov 10:35 – 10:50
ePoster	Population pharmacokinetic analysis of dolutegravir in HIV/TB co-infected people with and without rifampicin	Rajendra Singh	PE35/9	Exhibition hall 6 Nov 12:45 – 20:00 7 Nov 9:00 – 18:00

				8 Nov 9:00 – 18:00
--	--	--	--	-----------------------

Juluca (dolutegravir/rilpivirine)

Format	Title of abstract	Author/ presenter	Abstract / poster number	Time (CET)/ location
ePoster	SWORD 1&2: Maintenance or improvement in renal function in PLWH through 148 weeks after switch to the dolutegravir + rilpivirine 2-drug regimen	Josep Llibre	PE32/11	Exhibition hall 7 Nov 9:00 – 18:00 8 Nov 9:00 – 18:00
ePoster	Comparison of a two-drug regimen (dolutegravir/rilpivirine) to standard three-drug regimens in virologically suppressed, treatment experienced individuals in the real world	Gerald Pierone	PE2/37	Exhibition hall 6 Nov 12:45 – 20:00 7 Nov 9:00 – 18:00 8 Nov 9:00 – 18:00

Fostemsavir

Format	Title of abstract	Author/ presenter	Abstract/ poster number	Time (CET)/ location
ePoster	Baseline and emergent genotypic and phenotypic results in HIV-1-infected, heavily treatment-experienced (HTE) participants meeting protocol-defined virologic failure (PDVF) criteria through Week 96 in the fostemsavir (FTR) phase 3 BRIGHT study	Peter Ackerman	PE17/6	Exhibition hall 7 Nov 12:30 – 13:15
ePoster	Impact of susceptibility scoring on virologic response in heavily treatment-experienced participants with HIV-1 receiving a fostemsavir-based antiretroviral regimen: results through Week 96 from the randomized cohort of the phase 3 BRIGHT study	Peter Ackerman	PE3/5	Exhibition hall 6 Nov 12:45 – 20:00 7 Nov 9:00 – 18:00 8 Nov 9:00 – 18:00

Triumeq (DTG/ABC/3TC)

Format	Title of abstract	Author/ presenter	Abstract/ poster number	Time (CET)/ location
ePoster	Real world data of using Triumeq (dolutegravir/abacavir/lamivudine (DTG/ABC/3TC): final outcomes of the 3-year German TRIUMPH cohort show	Nils Postel	PE2/57	Exhibition hall 6 Nov 12:45 – 20:00 7 Nov

	good virologic effectiveness and safety in clinical routine			9:00 – 18:00 8 Nov 9:00 – 18:00
--	---	--	--	---------------------------------------

Additional abstracts

Format	Title of abstract	Author/presenter	Abstract/poster number	Time (CET)/location
Oral	A simple tool to evaluate the effectiveness of HIV care for settings with gaps in data availability	Dorthe Raben	PS9/2	San Francisco 8 Nov 10:45 – 11:00
Oral	Uptake and discontinuation of integrase inhibitors (INSTIs) in the RESPOND cohort collaboration	Lauren Greenberg	PS8/7	Event hall 8 Nov 11:45 – 11:55
ePoster	Characterizations of weight gain following antiretroviral regimen initiation in treatment-naïve individuals living with HIV	Ricky Hsu	PE2/32	Exhibition hall 6 Nov 12:45 – 20:00 7 Nov 9:00 – 18:00 8 Nov 9:00 – 18:00
ePoster	How to RESPOND to modern challenges for people living with HIV: a new cohort collaboration	Bastian Neesgaard	PE2/33	Exhibition hall 6 Nov 12:45 – 20:00 7 Nov 9:00 – 18:00 8 Nov 9:00 – 18:00
ePoster	Virologic, immunologic and clinical outcomes in antiretroviral treatment (ART) naïve individuals in the RESPOND cohort collaboration	Amanda Mocroft	PE2/40	Exhibition hall 6 Nov 12:45 – 20:00 7 Nov 9:00 – 18:00 8 Nov 9:00 – 18:00
ePoster	PK/PD modelling of bnAbs for HIV treatments identifying knowledge gaps	Mark Baker	PE4/6	Exhibition hall 6 Nov 12:45 – 20:00 7 Nov 9:00 – 18:00 8 Nov 9:00 – 18:00

About cabotegravir

Cabotegravir is an investigational integrase inhibitor (INI) and is not approved by regulatory authorities anywhere in the world. Cabotegravir is being developed by ViiV Healthcare for the treatment and prevention of HIV. It is being evaluated as a long-acting formulation for intramuscular injection and also as a once-daily oral tablet for use as a lead-in, to establish the tolerability of cabotegravir prior to long-acting injection.

About rilpivirine long-acting

Rilpivirine long-acting is an investigational, prolonged-release suspension for intramuscular injection being developed by Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson, and is not approved by regulatory authorities anywhere in the world.

About rilpivirine

Rilpivirine is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI). It is authorised in the EU in combination with other antiretroviral medicinal products, for the treatment HIV-1.

About fostemsavir

Fostemsavir is an investigational prodrug of temsavir, an HIV-1 attachment inhibitor, and is not authorised by regulatory authorities anywhere in the world. Fostemsavir is being developed by ViiV Healthcare for the treatment of HIV-1-infected heavily treatment-experienced patients in combination with other antiretroviral agents.

About Dovato (dolutegravir/lamivudine)

Dovato (dolutegravir 50 mg/ lamivudine 300 mg tablets) is authorised in the EU for the treatment of HIV-1 infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.⁸

Dolutegravir/lamivudine is a once-daily, single-pill, two-drug regimen that combines the integrase strand transfer inhibitor (INSTI) dolutegravir (Tivicay, 50 mg) with the nucleoside analogue reverse transcriptase inhibitor (NRTI) lamivudine (Epivir, 300 mg).

In the US the Food and Drug Administration (FDA) authorised Dovato, a complete, once-daily, single-tablet regimen of dolutegravir (DTG) 50 mg and lamivudine (3TC) 300 mg for the treatment of HIV-1 infection in adults with no antiretroviral (ARV) treatment history and with no known resistance to either DTG or 3TC.⁹

Like a dolutegravir-based three-drug regimen, dolutegravir/lamivudine uses two drugs to inhibit the viral cycle at two different sites. INSTIs, like dolutegravir, inhibit HIV replication by preventing the viral DNA from integrating into the genetic material of human immune cells (T-cells). This step is essential in the HIV replication cycle and is also responsible for establishing chronic infection. Lamivudine is an NRTI that works by interfering with the conversion of viral ribonucleic acid (RNA) into deoxyribonucleic acid (DNA) which in turn stops the virus from multiplying.

Important Safety Information for Dovato (50mg dolutegravir/300mg lamivudine) tablets in the EU

The following Important Safety Information is based on the Summary of Product Characteristics for Dovato. Please consult the full Summary of Product Characteristics for all the safety information.

Dovato (50mg dolutegravir/300mg lamivudine)

Dovato is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.

The recommended dose of Dovato in adults and adolescents is one 50 mg/300 mg tablet once daily.

Method of administration

Oral use. Dovato can be taken with or without food.

Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Dose adjustments

A separate preparation of dolutegravir is available where a dose adjustment is indicated due to drug-drug interactions (e.g. rifampicin, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, St. John's wort, etravirine (without boosted protease inhibitors), efavirenz, nevirapine, or tipranavir/ritonavir. In these cases the physician should refer to the individual product information for dolutegravir.

Missed doses

If the patient misses a dose of Dovato, the patient should take Dovato as soon as possible, providing the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

Special warnings and precautions for use

Transmission of HIV

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Hypersensitivity reactions

Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dovato and other suspect medicinal products should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with Dovato or other suspect active substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Liver disease

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Dovato includes lamivudine, which is active against hepatitis B. Dolutegravir lacks such activity. Lamivudine monotherapy is generally not considered an adequate treatment for hepatitis B, since the risk for hepatitis B resistance development is high. If Dovato is used in patients co-infected with hepatitis B an additional antiviral is therefore generally needed. Reference should be made to treatment guidelines.

If Dovato is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

Patients with pre-existing liver dysfunction, including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are Cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia (often referred to as PCP). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, bisphosphonates, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients should be advised that dolutegravir, lamivudine or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Undesirable effects

The most frequently reported adverse reactions are headache (3%), diarrhoea (2%), nausea (2%) and insomnia (2%).

The most severe adverse reaction reported with dolutegravir was a hypersensitivity reaction that included rash and severe liver effects.

Tabulated list of adverse reactions is available in the full information leaflet.

Changes in laboratory biochemistries

Dolutegravir has been associated with an increase in serum creatinine occurring in the first week of treatment when administered with other antiretroviral medicinal products. Increases in serum creatinine occurred within the first four weeks of treatment with dolutegravir plus lamivudine and remained stable through 48 weeks. These changes are linked to the inhibiting effect of dolutegravir on renal tubular transporters of creatinine. The changes are not considered to be clinically relevant and do not reflect a change in glomerular filtration rate.

Co-infection with Hepatitis B or C

In the Phase III studies for the dolutegravir single agent, patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn.

Drug interactions

No drug interaction studies have been conducted using Dovato. Dovato contains dolutegravir and lamivudine, therefore any interactions identified for these individually are relevant to Dovato. No clinically significant drug interactions are expected between dolutegravir and lamivudine.

The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, St. John's wort, etravirine (without boosted protease inhibitors), efavirenz, nevirapine, or tipranavir/ritonavir.

Dovato should not be co-administered with polyvalent cation-containing antacids. Polyvalent cation-containing antacids are recommended to be taken 2 hours after or 6 hours before Dovato.

When taken with food, Dovato and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. If Dovato is administered under fasting conditions, supplements or multivitamins containing calcium, iron or magnesium are recommended to be taken 2 hours after or 6 hours before Dovato.

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of Dovato with metformin, to maintain

glycaemic control. Metformin is eliminated renally and, therefore, it is of importance to monitor renal function when co-treated with Dovato. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment (stage 3a creatinine clearance 45– 59 mL/min) and a cautious approach is recommended. Reduction of the metformin dose should be highly considered.

The combination of Dovato with cladribine is not recommended.

Dovato should not be taken with any other medicinal product containing dolutegravir or lamivudine, except where a dose adjustment of dolutegravir is indicated due to drug-drug interactions.

Other established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in the full information leaflet.

Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential (WOCBP) should undergo pregnancy testing before initiation of Dovato. WOCBP who are taking Dovato should use effective contraception throughout treatment.

Pregnancy

The safety and efficacy of a dual regimen has not been studied in pregnancy. Preliminary data from a surveillance study has suggested an increased incidence of neural tube defects (0.9%) in mothers exposed to dolutegravir (a component of Dovato) at the time of conception compared with mothers exposed to non-dolutegravir containing regimens (0.1%).

The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births (0.05-0.1%). As neural tube defects occur within the first 4 weeks of foetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy. Due to the potential risk of neural tube defects with dolutegravir, Dovato should not be used during the first trimester unless there is no alternative.

More than 1000 outcomes from second and third trimester exposure to dolutegravir in pregnant women indicate no evidence of increased risk of malformities and foeto/neonatal negative effects. However, as the mechanism by which dolutegravir may interfere in human pregnancy is unknown, the safety in use during the second and third trimester cannot be confirmed. Dovato should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

In animal reproductive toxicology studies with dolutegravir, no adverse development outcomes, including neural tube defects, were identified. Dolutegravir was shown to cross the placenta in animals.

A large amount of data on the use of lamivudine in pregnant women (more than 3000 outcomes from first trimester) indicates no malformative toxicity.

Animal studies showed lamivudine may inhibit cellular DNA replication (see section 5.3). The clinical relevance of these findings is unknown.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues, these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), and metabolic disorders (hyperlactatemia, hyperlipasemia). These reactions have often been transitory. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Breast-feeding

It is unknown whether dolutegravir is excreted in human milk. Available toxicological data in animals has shown excretion of dolutegravir in milk. In lactating rats that received a single oral dose of 50 mg/kg at 10 days postpartum, dolutegravir was detected in milk at concentrations typically higher than blood.

Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of lamivudine when administered to babies less than three months old.

It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

There are no data on the effects of dolutegravir or lamivudine on human male or female fertility.

Animal studies indicate no effects of dolutegravir or lamivudine on male or female fertility.

Effects on ability to drive and use machines

Dovato has no or negligible influence on the ability to drive and use machines. Patients should be informed that dizziness and somnolence has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of Dovato should be borne in mind when considering the patient's ability to drive or operate machinery.

Please refer to the full European Summary of Product Characteristics for [Dovato](#) [for full prescribing information](#), including contraindications, special warnings and precautions for use. For the US, please refer to the [US Prescribing Information](#).

Trademarks are owned by or licensed to the ViiV Healthcare group of companies.

About Juluca (dolutegravir/rilpivirine)

Juluca is ViiV Healthcare's first two-drug regimen (2DR), once-daily, single-pill that combines dolutegravir 50mg (ViiV Healthcare), the most widely prescribed integrase inhibitor (INI) worldwide, with the nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine 25mg (Janssen Sciences Ireland UC). Juluca was granted marketing authorisation by regulatory authorities in the United States in November 2017, the European Union and Canada in May 2018, and Australia in June 2018.^{10,11,12,13}

Juluca is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any NNRTI or INI.

Important Safety Information for Juluca (50mg dolutegravir/25mg rilpivirine) tablets in the EU:

Juluca (dolutegravir 50mg, rilpivirine 25mg) is contraindicated in any patient with hypersensitivity to the active substances dolutegravir or rilpivirine or to any of the excipients.

Juluca is contraindicated in patients taking:

- dofetilide
- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifampicin, rifapentine
- proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole
- the systemic glucocorticoid dexamethasone, except as a single dose treatment
- St John's wort (*Hypericum perforatum*)

Factors that decrease the exposure of the components of Juluca should be avoided. Juluca should not be taken with any other medicinal products containing dolutegravir or rilpivirine or antiretroviral medicinal products used for the treatment of HIV.

The safety and efficacy of Juluca has not yet been established in patients <18 years and/or in women who are pregnant. Use of Juluca in these patient populations is not recommended.

No dosage adjustment is required in patients with mild or moderate renal impairment. In patients with severe or end stage renal disease, the combination of Juluca with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. No data are available in subjects receiving dialysis although differences in pharmacokinetics are not expected in this population.

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). Juluca should be used with caution in patients with moderate hepatic impairment. No data are available in patients with severe hepatic impairment (Child-Pugh score C); therefore Juluca is not recommended in these patients.

Hypersensitivity reactions have been reported with dolutegravir and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Juluca should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with Juluca after the onset of hypersensitivity may result in a life-threatening allergic reaction.

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reconstitution, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Monitoring of liver function is recommended in patients with hepatitis B and/or C co-infection. No clinical data are available in patients with hepatitis B co-infection. Physicians should refer to current treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus. Limited data is available in patients with hepatitis C co-infection. A higher incidence of liver chemistry elevations (Grade 1) were observed in patients treated with dolutegravir and rilpivirine co-infected with hepatitis C compared to those who were not co-infected.

Patients should be advised that Juluca does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Although the aetiology is considered to be multifactorial (including corticosteroid use, bisphosphonates, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

At supra-therapeutic doses (75 and 300 mg once daily), rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG). Rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. Juluca should be used with caution when co-administered with medicinal products with a known risk of Torsade de Pointes.

Please refer to the full European Summary of Product Characteristics for [Juluca full prescribing information](#), including contraindications, special warnings and precautions for use. For the US, please refer to the [US prescribing information](#).

Juluca and Tivicay are trademarks owned by the ViiV Healthcare group of companies.

About Triumeq

Triumeq is a fixed-dose combination containing the INSTI dolutegravir and the NRTIs abacavir and lamivudine.

Two essential steps in the HIV life cycle are replication – when the virus turns its RNA copy into DNA – and integration – the moment when viral DNA becomes part of the host cell's DNA. These processes require two enzymes called reverse transcriptase and integrase. NRTIs and integrase inhibitors interfere with the action of the two enzymes to prevent the virus from replicating and further infecting cells.

Important Safety Information for Triumeq tablets in the EU:

Indications and Usage

Triumeq is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age weighing at least 40 kg.

Before initiating treatment with abacavir-containing products, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele. See full prescribing information for TIVICAY. Please consult the full Summary of Product Characteristics for the individual products for all the safety information.

Important Safety Information for TRIUMEQ

Hypersensitivity Reactions:

- Both abacavir and dolutegravir are associated with a risk for hypersensitivity reactions (HSR), and share some common features such as fever and/or rash with other symptoms indicating multi-organ involvement. Clinically it is not possible to determine whether a HSR with Triumeq would be caused by abacavir or dolutegravir.

Hypersensitivity reactions have been observed more commonly with abacavir, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately. The risk for abacavir HSR to occur is high for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a low frequency in patients who do not carry this allele.

Therefore, the following should always be adhered to:

- HLA-B*5701 status must always be documented prior to initiating therapy.
- Triumeq should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen.
- Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir-containing products
- Hypersensitivity to abacavir is a multi-organ clinical syndrome

- Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir, although hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele
- Triumeq must be stopped without delay, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with Triumeq after the onset of hypersensitivity may result in an immediate and life-threatening reaction. Clinical status including liver aminotransferases and bilirubin should be monitored.
- After stopping treatment with Triumeq for reasons of a suspected HSR, Triumeq or any other medicinal product containing abacavir or dolutegravir must never be re-initiated.
- Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation and may include life-threatening hypotension and death.
- In order to avoid restarting abacavir and dolutegravir, patients who have experienced a suspected HSR should be instructed to dispose of their remaining Triumeq tablets.

Exacerbations of Hepatitis B:

- Severe acute exacerbations of HBV have been reported in patients who are co-infected with HBV and HIV-1 and have discontinued lamivudine, a component of TRIUMEQ. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients of Triumeq

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions:

- Hypersensitivity reactions have been reported with dolutegravir and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury.
- Clinically, it is not possible to determine whether a hypersensitivity reaction with TRIUMEQ would be caused by abacavir or dolutegravir.
- Discontinue TRIUMEQ immediately if signs or symptoms of hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Liver disease

The safety and efficacy of Triumeq has not been established in patients with significant underlying liver disorders. Triumeq is not recommended in patients with moderate to severe hepatic impairment.

Patients with pre-existing liver dysfunction, including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients with chronic hepatitis B or C

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Triumeq includes lamivudine, which is active against hepatitis B. Abacavir and dolutegravir lack such activity. Lamivudine monotherapy is generally not considered an adequate treatment for hepatitis B, since the risk for hepatitis B resistance development is high. If Triumeq is used in patients co-infected with hepatitis B an additional antiviral is, therefore, generally needed. Reference should be made to treatment guidelines.

If Triumeq is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART.

Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia (often referred to as PCP). Any inflammatory symptoms

should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection.

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues, these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), and metabolic disorders (hyperlactatemia, hyperlipasemia). These reactions have often been transitory. Some late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown aetiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Myocardial infarction

Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing Triumeq, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, bisphosphonates, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-

term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients should be advised that Triumeq or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Drug resistance

Since the recommended dose of dolutegravir is 50 mg twice daily for patients with resistance to integrase inhibitors, the use of Triumeq is not recommended for patients with integrase inhibitor resistance.

Lactic Acidosis and Severe Hepatomegaly with Steatosis:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including abacavir and lamivudine. Female sex and obesity may be risk factors in patients treated with nucleoside analogues

Embryofetal Toxicity:

- Women of childbearing potential (WOCBP) should undergo pregnancy testing before initiation of Triumeq. WOCBP who are taking Triumeq should use effective contraception throughout treatment.
- Avoid use of dolutegravir, a component of TRIUMEQ, at the time of conception through the first trimester due to the risk of neural tube defects

Myocardial Infarction (MI):

- Several observational studies have reported an association with the use of abacavir and the risk of MI; meta-analyses of randomized controlled clinical trials did not show increased risk. To date, there is no established biological mechanism to explain a potential increase in risk. In totality, the available data show inconsistency; therefore, evidence for a causal relationship between abacavir and the risk of MI is inconclusive
- The underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (eg, hypertension, hyperlipidemia, diabetes mellitus, smoking)

ADVERSE REACTIONS
The most common adverse reactions (incidence $\geq 2\%$, Grades 2-4) in treatment-naïve adults receiving TRIUMEQ were insomnia (3%), headache (2%), and fatigue (2%).

DRUG INTERACTIONS

- Coadministration of TRIUMEQ with drugs that induce or inhibit UGT1A1 and/or CYP3A may affect plasma concentrations
- Triumeq should not be co-administered with polyvalent cation-containing antacids. Triumeq is recommended to be administered 2 hours before or 6 hours after these medicinal products.
- Triumeq is recommended to be administered 2 hours before or 6 hours after taking supplements or multivitamins containing calcium, iron or magnesium.
- Consult the full Prescribing Information for TRIUMEQ for more information on potentially significant drug interactions, including clinical comments

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** There are insufficient human data on the use of TRIUMEQ during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. An Antiretroviral Pregnancy Registry has been established. Avoid use of dolutegravir, a component of TRIUMEQ, at the time of conception through the first trimester of pregnancy. If planning a pregnancy or if pregnancy is confirmed while taking dolutegravir during the first trimester, if possible, switch to an alternative regimen
- **Lactation:** Breastfeeding is not recommended due to the potential for HIV-1 transmission, developing viral resistance in HIV-positive infants, and adverse reactions in a breastfed infant
- **Females and Males of Reproductive Potential:** Perform pregnancy testing before initiation of dolutegravir. Advise adolescents and adults of childbearing potential to consistently use effective contraception while taking dolutegravir
- **Patients with Impaired Renal Function:** TRIUMEQ is not recommended in patients with creatinine clearance <50 mL/min
- **Patients with Impaired Hepatic Function:** If a dose reduction of abacavir is required for patients with mild hepatic impairment, then the individual components of TRIUMEQ should be used

Please refer to the full European Summary of Product Characteristics for [Triumeq full prescribing information](#), including contraindications, special warnings and precautions for use. For the US, please refer to the [US prescribing information](#).

About ViiV Healthcare

ViiV Healthcare is a global specialist HIV company established in November 2009 by GlaxoSmithKline (LSE: GSK) and Pfizer (NYSE: PFE) dedicated to delivering advances in treatment and care for people

living with HIV and for people who are at risk of becoming infected with HIV. Shionogi joined in October 2012. The company's aim is to take a deeper and broader interest in HIV/AIDS than any company has done before and take a new approach to deliver effective and innovative medicines for HIV treatment and prevention, as well as support communities affected by HIV.

For more information on the company, its management, portfolio, pipeline and commitment, please visit <https://viiivhealthcare.com/en-gb/>.

About GSK

GSK is a science-led global healthcare company with a special purpose: to help people do more, feel better, live longer. For further information please visit www.gsk.com.

ViiV Healthcare media enquiries:	Melinda Stubbee	+1 919 491 0831
	Patricia O'Connor	+44 (0) 20 8047 5982
GSK Global media enquiries:	Simon Steel	+44 (0) 20 8047 5502
	Kristen Neese	+1 804 217 8147
Analyst/Investor enquiries:	Sarah Elton-Farr	+44 (0) 20 8047 5194
	Danielle Smith	+44 (0) 20 8047 0932
	James Dodwell	+44 (0) 20 8047 2406
	Jeff McLaughlin	+1 215 751 7002

References

¹ Quercia R, Orkin C, D'Amico R, et al. Outcomes for women in phase 3 trials of long-acting cabotegravir + rilpivirine: pooled ATLAS & FLAIR week 48 results.

² Ackerman P, Gartland M, Chabria S, et al. Baseline and emergent genotypic and phenotypic results in HIV-1-infected, heavily treatment-experienced (HTE) participants meeting protocol-defined virologic failure (PDVF) criteria through week 96 in the fostemsavir (FTR) phase 3 BRIGHT study.

³ Ackerman P, Llamoso C, Pierce A. Impact of susceptibility scoring on virologic response in heavily treatment-experienced participants with HIV-1 receiving a fostemsavir-based antiretroviral regimen: results through week 96 from the randomized cohort of the phase 3 BRIGHT study.

⁴ Underwood M, Urbaityte R, Wang R, et al. Assessments of very low-level HIV replication for dolutegravir + lamivudine (DTG+3TC) vs dolutegravir + tenofovir disoproxil/emtricitabine (DTG+TDF/FTC) in the GEMINI 1 & 2 studies through week 96.

⁵ Ait-Khaled M, Nascimento MC, Pappa KA, et al. Switching to DTG/3TC fixed dose combination (FDC) is non-inferior to continuing a TAF-based regimen (TBR) through 48 weeks: subgroup analyses from the TANGO study..

⁶ Wang R, Horton J, Wright J, et al. Switching from a 3-drug tenofovir alafenamide (TAF)-based regimen (TBR) to a 2-drug dolutegravir/lamivudine (2DR, DTG/3TC FDC) was not associated with a higher frequency of intermittent viremia in suppressed patients in the TANGO study..

⁷ Pierone G, Schulman K, Fusco J, et al. Comparison of a two-drug regimen (dolutegravir/rilpivirine) to standard three-drug regimens in virologically suppressed, treatment experienced individuals in the real world.

⁸ Dovato EU Summary of Product Characteristics, 2019.

⁹ Dovato US prescribing information, 2019.

¹⁰ Juluca US prescribing information, 2017.

¹¹ Juluca EU Summary of Product Characteristics, 2018.

¹² Health Canada. Juluca certified product information document. 18 May 2018.

¹³ Australian Government. Department of Health Therapeutic Goods Administration. Juluca Product Information - ARTG ID 291356.